REMARKS

In the Action, the examiner rejected claims 45-55 under 35 USC 112, 1st paragraph as assertedly lacking enablement, and under 35 USC 103 (a) as assertedly obvious in view of Nichol et al., US Patent 4,587,340 (hereinafter "Nichol") and JP05194229.

I. The rejection of claims 45-55 under 35 USC §112, 1st paragraph, as assertedly lacking enablement should be withdrawn

The examiner rejected claims 45-55 as allegedly lacking enablement, asserting that the specification failed to teach how to make and use the compounds useful in the claimed methods. The examiner contends that the specification lacks specific conditions or starting material or reaction conditions sufficient to teach one of ordinary skill how to synthesize the claimed compounds. The examiner further states that even if the reaction schemes were taught in the art, the method of synthesis is essential subject matter which cannot be incorporated by reference (page 5 of the action). Applicants respectfully disagree.

Although a considerable amount of work may be required to carry out the invention, when such experimentation is routine, the experimentation is not "undue," In re Wands, 858 F2d 731 (Fed. Cir.1988). "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F2d 220, 224 (CCPA 1977).

"[A] patent need not teach, and preferably omits, what is well known in the art" See 2164.05(a); Hybritech Inc. v Monoclonal Antibodies Inc., 802 F. 2d 1367, 1384 (Fed. Cir. 1986). In this case, it had been long known in the art how to synthesize tetrahydrobiopterin and other pterin analogs. See e.g., Nichol et al., US Patent 4,587,340, which teaches methods to make biopterin analogs starting from a 2-amino 5,6,7,8 tetrahydro-pteridinone with modification at the 6 carbon (see Nichol, col. 1, lines 18-41). Also, the specification teaches that compositions useful in the present methods have been described previously in EP 0164964 and US 4,665,182 (page 24 of the translated text submitted 3/20/06). These disclosures teach chemical synthesis of acylated tetrahydrobiopterin derivatives and biopterin derivatives, respectively. These two publications have been available for over 15 years before the present application. Thus, the compounds of Formula I and methods of making them have been known in the art for many years, and methods of making these compounds using routine chemical synthesis methods have been taught in the art. The examiner even

admits that the art had provided a detailed blueprint for making and using modified compounds of the general formula as claimed, the sequence of which is provided by Nichol and JP05194229, and the steps of which are routine to one of ordinary skill (pages 13 to 14 of the Action).

One of ordinary skill in the art of chemical synthesis would readily recognize that these types of compounds recited in the claims are made using standard chemical synthesis techniques as disclosed in the art, e.g., EP 0164964 and US 4,665,182. Thus, the compounds and methods of making the compounds were readily available in the art and could have been modified by a person of ordinary skill using standard chemical techniques. What is commonly known in the art need not be included in the specification (See Hybritech v Monoclonal Antibody, Inc., *supra*). Because the level of skill in the art of making biopterin analogs used in the present methods is high, and methods to make these analogs have been previously disclosed in the art, one of ordinary skill could have readily made the compounds for use in the claimed methods, and the specification is sufficiently enabled such that one of ordinary skill can carry out the methods of the invention.

The examiner argues that even if one of ordinary skill could have made the compounds recited in the claims based on knowledge in the art, the manner of making them is essential subject matter which cannot be incorporated by reference. However, material is only essential if ***"one skilled in the art could not develop [the missing information] without undue experimentation*** *(emphasis added).* MPEP 2164.06(a) ("doubt arises about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why the missing information is needed . . .")

Applicants submit that in the present case, synthesis procedures for the type of compounds in Formula I recited in the claims has been ***routine*** for over 15 years, such that reproducing exact chemical reaction schemes is not necessary to enable synthesis. Such well known material is not essential, need not be included and in fact is ***preferably omitted.*** See MPEP 2164.05(a).

The claims are directed to a method of treating protein tolerance deficiencies due to mutations in the PAH gene using particular family of compounds, and not to the chemical

compounds themselves. The examples in the specification describe methods of treating subjects having mutations in the PAH gene with compounds in the recited formula to correct protein tolerance deficiencies. Thus, the subject matter of the claims is described in the specification and the disclosure teaches one of ordinary skill to carry out the methods of the invention. The manner of synthesizing chemical compounds using routine techniques well-known to one of ordinary skill is not essential to carrying out the claimed method, and therefore the requirement that the specification describe chemical reaction schemes useful to synthesize compounds that are well-known in the art should be withdrawn.

II. The rejection of claims 45-55 under 35 USC §103 should be withdrawn

The examiner rejected claims 45 -55 as allegedly obvious in view of Nichol and JP 05194229, asserting that one of ordinary skill would have readily modified the teachings of Nichol and JP05194229 to arrive at the present method for treating conditions of reduced protein tolerance using the recited compounds. Applicants respectfully disagree.

The claims are directed to a method of treating conditions with lowered protein tolerance due to reduced phenylalanine oxidation without deficiency of cofactor tetrahydrobiopterin (BH4), said conditions caused by mutations in the phenylalanine hydroxylase gene, wherein the agent used is of the formula recited in the claims. Tetrahydrobiopterin (BH4) is an exemplary compound useful in the methods of the invention.

The examiner has failed to establish a *prima facie* case of obviousness since all the elements of the claimed invention are not disclosed in the cited art. Moreover, there is no motivation to combine the teachings of Nichol and JP05194229 to arrive at the present invention, nor is there a reasonable expectation of success that one of ordinary skill would have arrived at the present invention based on the teachings in the art.

Nichol discloses use of pterin analogs, which are analogs of BH4, and use of these analogs to treat Parkinsonism and BH4 deficiency. Patients with BH4 deficiency are unable to synthesize or recycle adequate amounts of BH4. In contrast, patients with PAH mutations have a defective PAH enzyme that is unable to degrade phenylalanine efficiently, thus resulting in elevated levels of phenylalanine in blood and consequently elevated levels of phenylalanine excreted into urine (phenylketonuria, or PKU). Nichol neither discloses nor suggests that BH4 would be beneficial to treat phenylketonuria resulting from a mutation in the PAH gene, which is a different basis for disease compared to BH4 deficiency.

JP05194229 discloses use of a pterin agent to treat nervous diseases, such as concentration disorders, akinesia, shivering, etc. The agents in JP05194229 are similar to those agents recited in the claimed method. However, JP05194229 neither discloses nor suggests that the pterin agents are useful to treat any disorder other than a nervous disorder, let alone treat PKU resulting from a mutation in the PAH gene and not from BH4 deficiency.

Neither Nichols nor JP05194229, taken alone or in combination, discloses treatment of PKU resulting from a mutation in a PAH gene. Further, one of ordinary skill in the art would not have been motivated by the cited art, nor had a reasonable expectation of success based on the cited art, to arrive at the present invention. Neither Nichol nor JP05194229 describe what role BH4 would play in correcting a mutation in the PAH gene.

Moreover, neither Nichol nor JP05194229 disclose the specific pairs of PAH mutations recited in claim 45 or their correlation with high sensitivity and efficiency of BH4-based treatment of PKU due to PAH mutations. Thus, one of ordinary skill would not have been motivated to treat these conditions with BH4 or had a reasonable expectation of success at treating protein deficiencies arising from mutations in the PAH gene when the art did not recognize that BH4 was useful to treat such conditions.

For the foregoing reasons, the examiner has failed to establish a *prima facie* case of obviousness, and the rejection of claims 45-55 as obvious in view of Nichol and JP05194229 should be withdrawn.

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